Viral Hepatitis

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This disorder is caused by at least five pathogenic viruses recognized to date: hepatitis A, B, C, D, and E viruses. Many other viruses can cause hepatitis, usually as one component of a multisystem disease; these include herpes simplex virus (HSV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), varicella-zoster virus, HIV, rubella, adenoviruses, enteroviruses, parvovirus B19, and arboviruses. Hepatitis G virus (GBV) and transfusion transmissible virus (TTV) often infect the liver as a co-infection with another hepatotropic virus, and may produce acute or chronic viremia but rarely produce hepatocellular injury on their own.

Often what brings the patient to medical attention is clinical icterus, which, in hepatitis, is a mixed or conjugated (direct) reacting hyperbilirubinemia.
In the **newborn period,** infection is a common cause of direct reacting hyperbilirubinemia; the infectious cause is either a bacterial agent (Escherichia coli, Listeria) or one of the non-hepatotropic viruses (HSV, enteroviruses, CMV). Metabolic and anatomic causes (tyrosinemia, biliary atresia, choledochal cysts) should always be excluded.
In later **childhood,** extrahepatic obstruction (gallstones, primary sclerosing cholangitis, pancreatic pathology), inflammatory conditions (autoimmune hepatitis, juvenile rheumatoid arthritis, Kawasaki disease, immune dysregulation), infiltrative disorders (malignancies), toxins/medications, metabolic disorders (Wilson disease, cystic fibrosis), and infection (EBV, varicella, malaria, leptospirosis, syphilis) should be ruled out.

Pathogenesis;

The acute response of the liver to hepatotropic viruses involves a direct cytopathic as well as an immune-mediated injury. The entire liver is involved. Necrosis when present, is usually most marked in the centrilobular areas. An acute mixed inflammatory infiltrate predominates in the portal areas but also affects the lobules. The lobular architecture remains intact, although balloon degeneration and necrosis of single or groups of parenchymal cells occur frequently. Fatty change is rare except with HCV infection. Bile duct proliferation but not bile duct damage is common. Diffuse Kupffer cell hyperplasia is noticed in the sinusoids. Neonates often respond to hepatic injury by forming **giant cells.**
In **fulminant hepatitis,** parenchymal collapse occurs on the just described background. With recovery, the liver returns to its morphologic normal within 3 mo of the acute infection. If chronic hepatitis develops, the inflammatory infiltrate settles in the periportal areas and often leads to progressive scarring; both of these hallmarks of chronic hepatitis are seen in cases of HBV and HCV.

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Hepatitis A

Hepatitis A virus (HAV) is the most prevalent of the five viruses worldwide. This virus is also responsible for most forms of acute and benign hepatitis; although fulminant hepatic failure can occur, it is rare and occurs more often in adults than in children.

Etiology

HAV is an RNA virus, a member of the picornavirus family. It is heat stable and has limited host range—namely, the human and other primates.

Epidemiology;

HAV infection occurs throughout the world but is most prevalent in the developing countries. HAV is highly contagious. Transmission is almost always by person-to-person contact through the fecal-oral route. Parenteral transmission occurs rarely The mean incubation period for HAV is ≈3 wk. Fecal excretion of the virus starts late in the incubation period, reaches its peak just before the onset of symptoms, and resolves by 2 wk after the onset of jaundice in older subjects. The duration of viral excretion is prolonged in infants. The patient is therefore contagious before clinical symptoms are apparent, and remains so until viral shedding stops.

Clinical manifestations;

HAV is responsible for acute hepatitis only. Often, this is an anicteric illness, with clinical symptoms indistinguishable from other forms of viral gastroenteritis, particularly in young children.

The illness is much more likely to be symptomatic in older adolescents or adults, in patients with underlying liver disorders, and in those who are immunocompromised. It is characteristically an acute febrile illness with an abrupt onset of anorexia, nausea, malaise, vomiting, and jaundice. The typical duration of illness is 7–14 days.

Other organ systems can be affected during acute HAV infection. Regional lymph nodes and the spleen may be enlarged. The bone marrow may be moderately hypoplastic, and aplastic anemia has been reported. Small intestinal tissue may show changes in villous structure, and ulceration of the gastrointestinal tract can occur, especially in fatal cases. Acute pancreatitis and myocarditis have been reported, though rarely, and nephritis, arthritis, vasculitis, and cryoglobulinemia can result from circulating immune complexes.

Diagnosis

Acute HAV infection is diagnosed by detecting antibodies to HAV, specifically, **anti-HAV (immunoglobulin [Ig] M) by radioimmunoassay** or, rarely, by identifying viral particles in stool. A viral polymerase chain reaction (**PCR**) assay is available for research use . **Anti-HAV** is detectable when the symptoms are clinically apparent, and remains positive for 4–6 mo after the acute infection. **A neutralizing anti-HAV (IgG) is usually detected within 8 wk of symptoms onset**, and is measured as part of a total anti-HAV in the serum, conferring long-term protection. The **virus is excreted in stools from 2 wk before to 1 wk after the onset of illness**. Rises in ALT, AST, bilirubin, ALP, 5′-nucleotidase, and GGT are almost universally found and do not help to differentiate the cause of hepatitis.

Complications;

Although most patients achieve full recovery, two distinct complications can occur:
1-Acute liver failure (ALF) from HAV infection, a rare but not infrequent complication of HAV. Those at risk for this complication are adults, but also patients with underlying liver disorders or those who are immunocompromised. The height of

HAV viremia may be linked to the severity of hepatitis. In endemic areas of the world, HAV constitutes up to 40% of all cases of pediatric ALF.

2-HAV can progress to a prolonged cholestatic syndrome that waxes and wanes over multiple months. Pruritus and fat malabsorption are problematic and require symptomatic support with antipruritic medications and fat-soluble vitamins. This syndrome occurs in the absence of any liver synthetic dysfunction and resolves with no sequelae.

Treatment;

There is no specific treatment for hepatitis A. Supportive treatment consists of intravenous hydration as needed and antipruritic agents and fat-soluble vitamins for the prolonged cholestatic form of disease. Serial monitoring for signs of acute liver failure and early referral to a transplantation center can be lifesaving.

Prevention;

Patients infected with HAV are contagious for 2 wk before and about 7 days after the onset of jaundice and should be excluded from school, child care, or work during this period. Careful handwashing is necessary, particularly after changing diapers and before preparing or serving food. In hospital settings, contact and standard precautions are recommended for 1 wk after onset of symptoms.

Vaccine.

The availability of two inactivated, highly immunogenic, and safe HAV vaccines has had a major impact on the prevention of HAV infection. Both vaccines are approved for children >1 yr of age. They are administered intramuscularly in a two-dose schedule, with the 2nd dose given 6–12 mo after the 1st dose. Seroconversion rates in children exceed 90% after an initial dose and approach 100% after the 2nd dose.. HAV vaccine can be administered simultaneously with other vaccines at separate sites. For persons >1 yr of age, vaccine is preferable to immunoglobulin for pre-exposure prophylaxis Greater consideration is being given, however, to other at-risk groups, including: (**1**) children >1 yr of age in defined and circumscribed communities with endemic rates or periodic outbreaks of HAV infection (e.g., Native Americans or Alaskan Natives); (**2**) patients with chronic liver disease; **(3**) individuals at occupational risk of exposure; and (**4**) persons with clotting factors and immune disorders. universal vaccination is recommended for all children >1 yr of age. Mass immunization of school children has been used when epidemics have been school centered..

Immunoglobulin (Ig).

Indications for intramuscular administration of Ig include pre-exposure and postexposure prophylaxis . Intravenous Ig is likely to be effective against HAV infection, but appropriate dose, efficacy, and duration of protection have not been defined. Ig is recommended for pre-exposure prophylaxis for all susceptible travelers to countries where HAV is endemic. For children >2 yr of age, HAV immunization is preferred if the interval before departure is >1 mo after dose 1. Ig as prophylaxis in postexposure situations is used for: (1) household and sexual contacts of HAV cases; (2) newborn infants of HAV-infected mothers; (3) child-care center staff, employees, children, and their household contacts during an outbreak; and (4) outbreaks in institutions and hospitals.

Prognosis;

The prognosis is excellent, with no long-term sequelae. The only feared complication is ALF. HAV infection remains a cause of major morbidity, however, and has a high socioeconomic impact during epidemics and in endemic areas.

Hepatitis B

Etiology

HBV is a member of the Hepadnaviridae family. The surface of the virus includes particles designated hepatitis B surface antigen (HBsAg). The inner portion of the virion contains hepatitis B core antigen (HBcAg). Replication of HBV occurs in the liver but also occurs in the lymphocytes, spleen, kidney, and pancreas.

Epidemiology;

HBV has a worldwide spread. HBV is present in high concentrations in blood, serum, and serous exudates and in moderate concentrations in saliva, vaginal fluid, and semen; efficient transmission occurs through blood exposure and sexual contact. Risk factors for HBV infection in children and adolescents include intravenous acquisition by drugs or blood products, acupuncture or tattoos, sexual contact, institutional care, and intimate contact with carriers.

The risk of developing **chronic HBV** infection, **defined as** being positive for HBsAg for >6 mo, is inversely related to age of acquisition. This risk of chronic infection is 90% in children <1 yr; the risk is 30% for those 1–5 yr and 2% for adults. Chronic infection is associated with the development of chronic liver disease, as well as hepatocellular carcinoma.

Pathogenesis

The 1st step in the process of **acute hepatitis** is infection of hepatocytes by HBV, resulting in expression of viral antigens on the cell surface. The mechanism for development of **chronic hepatitis** is less well understood. Although end-stage liver disease rarely develops, the inherent hepatocellular carcinoma risk is very high, possibly related, in part, to uncontrolled viral replication cycles.

Immune-mediated mechanisms are also involved in the **extrahepatic conditions** that can be associated with HBV infections. **Circulating immune complexes** containing HBsAg can occur in patients who develop associated polyarteritis nodosa, membranous or membranoproliferative glomerulonephritis, polymyalgia rheumatica, leukocytoclastic vasculitis, and Guillain-Barré syndrome.

Clinical manifestations;

Many acute cases of HBV infection in children are asymptomatic. The usual acute symptomatic episode is similar to that of HAV and HCV infections but may be more severe and is more likely to include involvement of skin and joints. The 1st biochemical evidence of HBV infection is elevation of ALT levels, which begin to rise just before development of lethargy, anorexia, and malaise, which occurs about 6–7 wk after exposure. The illness may be preceded in a few children by a serum sickness–like prodrome marked by arthralgia or skin lesions, including urticarial, purpuric, macular, or maculopapular rashes. Papular acrodermatitis, the Gianotti-Crosti syndrome, may also occur. Other extrahepatic conditions associated with HBV infections in children include polyarteritis, glomerulonephritis, and aplastic anemia. Jaundice, which is present in ≈25% of infected individuals, usually begins ≈8 wk after exposure and lasts for ≈4 wk. In the usual course of resolving HBV infection, symptoms are present for 6–8 wk. The percentage of children in whom clinical evidence of hepatitis develops is higher for HBV than for HAV, and the rate of ALF is also greater. Most patients do recover, but the "**chronic carrier state**" complicates up to 10% of cases acquired in adulthood. Chronic hepatitis cirrhosis and hepatocellular carcinoma are seen with chronic infection.

On **physical examination**, symptomatic infection results in icteric skin and mucous membranes. The liver is usually enlarged and tender to palpation and percussion. Splenomegaly and lymphadenopathy are common. Clinical signs of altered sensorium

and hyper-reflexivity should be carefully looked for, as they mark the onset of encephalopathy and ALF.

Diagnosis

Routine screening for HBV infection requires assay of at least **three** serologic markers (**HBsAg, anti-HBc, anti-HBs**). HBsAg is the 1st serologic marker of infection to appear and is found in almost all infected persons; its rise closely coincides with the onset of symptoms. Because HBsAg levels fall before symptoms wane, IgM antibody to HBcAg (anti-HBc IgM) helps to identify acute infection, as it rises early after infection and remains positive for many months before being replaced by anti-HBc IgG, which persists for years. **Anti-HBc is the most valuable single serologic marker of acute HBV infection because** it is present almost as early as HBsAg and **continues t**o be present later in the course of the disease when HBsAg has disappeared. Anti-HBs marks serologic recovery and protection. Only anti-HBs is present in persons immunized with hepatitis B vaccine, whereas both anti-HBs and anti-HBc are detected in persons with resolved infection. **HBeAg is present in active acute or chronic infections and is a marker of infectivity.** The development of anti-HBe marks improvement and is a goal of therapy in chronically infected patients. HBV DNA can be detected in the serum of acutely infected patients and chronic carriers. High DNA titers are seen in patients with HBeAg, and typically fall once anti-HBe develops.

Complications

ALF with coagulopathy, encephalopathy, and cerebral edema occurs more frequently with HBV than with the other hepatotropic viruses. Mortality due to ALF is >30%. Liver transplantation is the only effective intervention; supportive care aimed at sustaining patients and early referral to a liver transplantation center can be lifesaving. HBV infection can also result in **chronic hepatitis,** which can lead to **cirrhosis**, end-stage liver disease complications, and primary **hepatocellular carcinoma.**
Membranous glomerulonephritis with deposition of complement and HBeAg in glomerular capillaries is a rare complication of HBV infection.

Treatment;

No currently available medical therapy is reliably successful in the majority of persons infected with HBV. Treatment of the acute infection is largely supportive. Interferon-α-2b (IFN-α2b) and lamivudine (synthetic nucleoside analog) are the current therapies approved for treatment of **chronic** hepatitis B in adults >18 yr of age with compensated liver disease and HBV replication. IFN-α2b has also been used in children, with long-term eradication rates similar to the 25% rate reported in adults..

Prevention;

Hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) are available for prevention of HBV infection. Household, sexual, and needle-sharing contacts should be identified and vaccinated if they are susceptible to HBV infection. Children with HBV should not be excluded from school, play, child care, or work, unless they are prone to biting. All individuals positive for HBsAg should be reported to the state or local health department, and chronicity is diagnosed if they remain positive past 6 mo.

Prognosis; In general, the outcome after acute HBV infection is favorable, despite a risk of ALF. The risk of developing chronic infection brings the risks of liver cirrhosis and hepatocellular carcinoma to the forefront. Perinatal transmission leading to chronicity is responsible for the high incidence of hepatocellular carcinoma in young adults in the endemic areas. Importantly, HBV infection and its complications are effectively controlled with vaccination.